ReedSmith

Areta L. Kupchyk
Direct Phone: 202.414.9362
Email: akupchyk@reedsmith.com

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Reed Smith LLP
1301 K Street, N.W.
Suite 1100 – East Tower
Washington, D.C. 20005-3373
202.414.9200
Fax 202.414.9299

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Food and Drug Administration
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CITIZEN PETITION

The undersigned, on behalf of Jerome Stevens Pharmaceuticals, Inc. ("JSP"), submits this petition under § 505 of the Federal Food, Drug and Cosmetic Act ("FDCA") and 21 C.F.R. §§ 10.25 and 10.30. JSP requests that the Commissioner of the Food and Drug Administration (FDA) take the actions described below to establish guidance and clarify requirements for abbreviated new drug applications (ANDAs) with regard to levothyroxine sodium products.

This petition raises issues that are important for public health. Levothyroxine is the leading treatment for hypothyroidism and the management of thyroid cancer. It is prescribed annually to more than 13 million Americans (nearly 1 out of every 19). The drug is safe and effective only when administered in precise doses and when manufactured consistently and within specific potency ranges. FDA has documented that manufacturing processes vary with significant variability between drug-makers and product lots. *See* 62 Fed. Reg. 43,535 (Aug. 14, 1997). A small and unexpected difference in potency may present a serious health hazard in patients with coronary heart disease, cancer, and in pediatric patients. Neither the patients who depend on these drugs, nor the clinicians who prescribe them, can risk the uncertainty of receiving a generic substitute that is not manufactured with the same degree of consistency and accuracy as the reference listed drug.

While several orally administered levothyroxine products have been approved by the FDA pursuant to new drug applications (NDAs) submitted under § 505(b)(2) of the FDCA, FDA approved the first ANDA under § 505(j) of the FDCA. That ANDA, submitted by Mylan Pharmaceuticals, was approved on June 5, 2002. To date, however, FDA has not expressly established guidance or specific

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review criteria for the submission of an ANDA for levothyroxine. FDA, addressing primarily 505(b)(2) applicants, issued guidance for levothyroxine drug applications generally. FDA's guidance was grounded on the conclusion that consistency in manufacturing and stability is critical for the production of a safe and effective levothyroxine product. Such concerns are no less important for a levothyroxine product approved under a 505(j) application. An ANDA for levothyroxine, therefore, must be subject to the same rigorous review standards as its 505(b)(2) counterpart. This means that ANDA applicants should be expected to demonstrate, in the same way that 505(b)(2) applicants have been required to demonstrate, that their levothyroxine products are consistently manufactured batch-to-batch and dose-to-dose. Ensuring consistent potency is critical for ensuring a safe product. FDA guidance should apply equally to ANDAs as it does to NDAs. This petition outlines the scientific and legal rationale for the agency to take such action.

ACTIONS REQUESTED

We respectfully request that you:

(1) Issue specific guidance for the submission of levothyroxine applications under § 505(j) of the FDCA consistent with current guidance and requirements for levothyroxine products submitted under § 505(b)(2) of the FDCA.

(2) Not approve any ANDA for levothyroxine sodium that fails to conform to the standards for review established for 505(b)(2) applicants.

(3) Immediately withdraw approval of the ANDA for levothyroxine submitted by Mylan Pharmaceuticals, Inc. if it did not meet the same standard for review applicable to 505(b)(2) applicants.

STATEMENT OF GROUNDS

I. Background

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T4). Thyroid hormones affect protein, lipid, and carbohydrate metabolism; growth; and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production. The hormones possess a cardiostimulatory effect that may be the result of a direct action on the heart.

Orally administered levothyroxine sodium has been used for over 40 years as replacement therapy in conditions such as cretinism, myxedema, nontoxic goiter, and hypothyroidism. These conditions are characterized by a diminished or absent thyroid function. They may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine is also used for replacement or supplemental

therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism. In addition, the drug is used to suppress the secretion of thyrotropin in the management of simple nonendemic goiter, chronic lymphocytic thyroiditis, and thyroid cancer. Levothyroxine is also used with antithyroid agents in the treatment of thyrotoxicosis to prevent goitrogenesis and hypothyroidism.

Thyroid replacement therapy requires that the dosage be established for each patient individually. The initial dose is typically small and is increased gradually until a clinically optimal response is achieved; thereby the appropriate dosage maintenance level is established. The initial dosage and the rate at which the dosage may be increased is determined by the age and general physical condition of the patient and the severity and duration of hypothyroid symptoms.

FDA recognized that:

> "[i]t is particularly important to increase the dose very gradually in patients with myxedema or cardiovascular disease to prevent precipitation of angina, myocardial infarction, or stroke. If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on one product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmias. In patients with coronary heart disease, *even a small increase in the dose of levothyroxine sodium may be hazardous.* * * * Because of the risks associated with overtreatment or undertreatment with levothyroxine sodium, *it is critical that patients have available to them products that are consistent in potency and bioavailability.*[1]

II. The Approval of Oral Levothyroxine Products

On August 14, 1997, FDA issued a Federal Register notice calling for the submission of new drug applications for levothyroxine products.[2] Because levothyroxine products were marketed in as many as 11 dosage strengths, which varied by only 12 µg, FDA recognized that variations in the amount of available active drug could affect both safety and effectiveness. In addition, FDA noted that the drug substance levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity. To address these concerns, FDA required § 505(b)(2) applicants to demonstrate that the various dosages they manufactured were dosage form equivalent.

> * * * *Unless the manufacturing process can be carefully and consistently controlled, orally administered levothyroxine sodium products may not be fully potent through the labeled expiration date, or be of consistent potency from lot to lot.* There is evidence from recalls, adverse drug experience reports, and inspection reports that *even when a physician consistently prescribes the same brand* of orally administered levothyroxine sodium, *patients may receive products of variable potency at a given dose.* Such variations in product potency present actual safety and effectiveness concerns. * * * Accordingly, any orally administered drug product containing levothyroxine sodium is a new drug under section 201(p) of the act (21 U.S.C. 321(p)) and is subject to the requirements of section 505 of the act. Manufacturers who wish to continue to market orally administered levothyroxine sodium products must submit [new drug] applications

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[1] 62 *Fed. Reg.* 43, 535, 43, 536 (Aug. 14, 1997).

[2] *Id.*

> as required by section 505 of the act and part 314 (21 CFR part 314). * * * A bioavailability study must be completed and submitted as part of an NDA, including a 505(b)(2) application, *in order to evaluate the safety and efficacy of these products.* [3]

III. FDA's Guidance for the Submission of Marketing Applications for Levothyroxine

In December 2000, FDA issued Guidance for "In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets." In addition to single dose bioavailability studies, FDA recommended that all applicants provide a Dosage-Form Proportionality Study to determine the dosage-form proportionality among the to-be-marketed tablet strengths of levothyroxine sodium. Levothyroxine is produced in 11 strengths (25, 50, 75, 88, 100, 112, 125, 137, 150, 200, and 300 μg).

In the same guidance, FDA further recommended that three strengths of tablets be studied that represent the low, middle (100 μg), and high strength of the formulations to be marketed. A multiple of each tablet strength should be given to detect T_4 above baseline levels, with a total dose for each treatment at 600 μg, which should be the same dose for each treatment.

In July 2001, FDA issued additional guidance for levothyroxine sodium NDA applicants. First, however, in this guidance FDA announced that after August 14, 2001, the agency would exercise its authority under § 314.101(d)(9) to refuse to file a 505(b)(2) application that is eligible for approval under § 505(j). Applicants seeking to market a levothyroxine sodium product after August 14, 2001 "should submit an abbreviated new drug application (ANDA)." Presumably, the recommendations following this announcement in the guidance applied to 505(j) applications. FDA's silence on this issue implies that the content of ANDAs for levothyroxine products should be the same as the content of the 505(b)(2) applications for levothyroxine. FDA recommended the submission of specific manufacturing data, including "6 months' long term stability data and 3 months' accelerated stability data." FDA also stated that "[p]rimary stability data should be generated according to guidance developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[4]." FDA did not state that the data for the manufacturing of an ANDA levothyroxine product should be different in any way from the manufacturing data for a 505(b)(2) application.

To date, FDA has not issued separate guidance for the submission of levothyroxine ANDAs. Existing guidance for ANDA submissions, however, provides recommendations that conflict with the FDA's recommendations for levothyroxine applications. For example, in FDA's August 18, 1995 Industry Letter to "All ANDA and AADA Applicants," FDA announced that it would accept for ANDAs the ICH recommendations for long-term room temperature conditions for stability studies – 25±2 degrees C, 60±5%RH, as well as "any studies conducted at the conditions it has recommended in the past, 25-30 degrees C/ambient humidity."

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[3] *Id.* (emphasis added).

[4] Q1A Stability Testing of New Drug Substances and Products (September 1994).

IV. FDA Should Grant the Relief Requested by This Petition

A. The Relief Requested is Appropriate Under the Specific Policies Established by the FDA for Levothyroxine Products

Levothyroxine sodium is an unstable drug substance. It is subject to potency and stability problems. FDA noted that, "[u]nless the manufacturing process can be carefully and consistently controlled, orally administered levothyroxine sodium products may not be fully potent through the labeled expiration date, or *be of consistent potency from lot to lot*. * * **Such variations in product potency present actual safety and effectiveness concerns*." Therefore, 505(b)(2) applicants were asked to provide, and they provided, *in vivo* dosage-form proportionality studies, as well as extensive stability studies based on ICH guidelines, to demonstrate the consistency of their products from batch-to-batch and from dose-to-dose.

As a 505(b)(2) applicant, JSP was directed by FDA to provide, among other things, data based on the following information:

1. A dosage form equivalence study utilizing three different strengths of levothyroxine (50, 100, and 300 μg) at a total dose of 600 μg.. The study involved two washout periods of 35 days following the first and second dose. The dosage equivalence study demonstrates proportional bioequivalence within the respective manufacture's levothyroxine product line.

2. ICH guidelines for storage conditions and stability, including three batches of the highest and lowest strengths, and two batches for the in-between strengths.

3. Three stability batches of each 11 drug strength (total of 33 batches for JSP) including full compendia testing and multipoint dissolution testing for all 33 batches.

A generic drug must show that it is the same as a reference listed drug. To that end, ANDA levothyroxine products must show that they too can produce a product that is within an acceptable potency range and is stable over time. To date, however, FDA has not issued guidance specifically for generic applicants of levothyroxine products. Nor has FDA published a rationale to recommend a lower review standard for approval of ANDA levothyroxine products. Current FDA guidance for ANDA applicants provides that:

(1) Stability and storage conditions may be based on either ICH standards or ambient conditions (which permits a fewer number of batches to show stability);[5]
(2) Only a single dose fasting in vivo bioequivalency study is recommended;[6] and

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[5] FDA Guidance: Industry Letter to All ANDA and AADA Applicants (August 18, 1995).

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(3) No dosage-form proportionality studies are recommended.

Mylan's ANDA for levothyroxine did not include a dosage-form proportionality study. FDA's Office of Generic Drugs (OGD), in response to an inquiry from Mylan on the needed data for a levothyroxine ANDA, advised Mylan to "conduct only a single-dose fasting *in-vivo* bioequivalency study [using] a 35 day washout period for a two-way crossover design. Alternatively [FDA recommended that Mylan could] use a parallel design with equal numbers of male and female subjects in each treatment group." Not only did FDA not require Mylan to conduct a dose-form proportionality study, OGD granted Mylan a waiver of *in-vivo* bioequivalency for lower strengths if, in part, Mylan showed a "proportional similarity in the formulations of all strengths."[7]

In vivo dosage-form proportionality studies were expected from all § 505(b)(2) applicants of levothyroxine products. FDA required such studies, as opposed to mere evidence of "proportional similarity in the formulations," because it recognized that the manufacturing process, as well as the formulation, has an effect on the consistency of a product batch-to-batch and dose-to-dose.[8] Without such studies, FDA could not determine whether a manufacturer was capable of making a consistent product within its own production line. Concerns about manufacturing to produce a consistently potent and stable product is of no less concern for a generic. Without such studies, FDA cannot determine whether Mylan, or any other generic manufacturer, is capable of making a consistent product within its own production line. Therefore, the same data should be expected in § 505(j) applications.

An ANDA applicant must show, among other things, that its product is the "same" as the reference listed drug with respect to the active ingredient, route of administration, dosage form, strength, and labeling.[9] With levothyroxine products, multiple strengths of the same brand are used to obtain the optimal dosage for each individual patient. "Sameness," therefore, must include a demonstration that a generic product's various strengths are dosage form equivalent. Because of the difficulty in

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[6] FDA Guidance for Industry, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (October 27, 2000).

[7] Letter from Gary Buehler, Acting Director of the Office of Generic Drugs, FDA, to Mylan Pharmaceuticals, Inc. (June 14, 2001).

[8] The persistent difficulties associated with the manufacture of levothyroxine are demonstrated by the numerous recalls of Levoxyl, a levothyroxine product manufactured and distributed by Jones Pharma, Inc., a wholly owned subsidiary of King Pharmaceuticals, Inc. Despite the submission of manufacturing data, including dosage form equivalency studies, Levoxyl has been recalled four times since it was approved under a 505(b)(2) application. Levoxyl recalls were initiated May 10, 2002, April 11, 2003, July 18, 2003, and most recently October 10, 2003. Persistent potency and stability problems do not support a ***lower*** standard for determining the ability of a manufacturer, generic or not, to produce a consistent product. If anything, the experience with Levoxyl demands that generics, ***at a minimum***, provide the same evidence of manufacturing consistency as 505(b)(2) applicants were required to provide to FDA.

[9] 21 U.S.C. § 505(j)(2)(A).

manufacturing a consistent levothyroxine product, merely showing a "proportional similarity in formulations" is not sufficient, as it was not sufficient for 505(b)(2) applicants. There is no reasonable basis, either legally or scientifically, to abandon this important criteria for ANDAs.

FDA should, therefore, issue guidance to clarify that a levothyroxine ANDA application must provide the same manufacturing data as required of 505(b)(2) applicants. In addition, FDA should not approve any ANDA application that fails to provide adequate manufacturing data, consistent with the review standards applied to 505(b)(2) applications for levothyroxine sodium products.

B. FDA has Grounds to Withdraw Approval of Mylan's ANDA.

FDA is authorized to withdraw approval of a drug application, after due notice and opportunity for a hearing, if there is post-approval evidence that the drug approved was not shown to be safe or lacks substantial evidence of effectiveness. The Act provides that FDA may withdraw approval if:

> . . . new evidence of clinical experience, not contained in such application or not available to [FDA] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to [FDA] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved...,[10]

or

> . . . on the basis of new information...evaluated together with the evidence available before [FDA] when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. . . ."[11]

FDA has an obligation to judge a drug's effectiveness and safety by contemporary scientific standards. FDA said that "[i]f those standards change to the extent that it is questionable whether a drug can be regarded as having been shown to be effective [or safe], FDA may under the act appropriately review the drug's [approval] status."[12]

Current scientific standards for the review of levothyroxine products, produced in as many as 11 strengths with as little as 12 µg difference in strength, requires a review of dosage form equivalency studies. Unlike many orally administered products, levothyroxine sodium is titrated to each individual patient in small increments using various dosage strengths to determine the optimal dosage. Unless the

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[10] 21 U.S.C. § 505(e)(2); 21 C.F.R. § 314.150(a)(2)(ii).

[11] 21 U.S.C. § 505(e)(3); 21 C.F.R. §314.150(a)(2)(iii)

[12] New Drug and Antibiotic Regulations, Final Rule, 50 *Fed. Reg.* 7452, 7488 (February 22, 1985)(discussion of comments regarding withdrawal of approval under 21 C.F.R.§ 314.150).

various strengths are dose proportional, a patient is at risk of being overdosed or underdosed in the course of titration and in dose maintenance. Consequently, such a drug product would, not only be ineffective, but also potentially dangerous for the patient. Dosage form equivalence studies, therefore, are essential for determining whether the generic levothyroxine is the same as the reference listed drug.

Based on the information available to FDA today, FDA should issue guidance to clarify what data is necessary to establish that a generic levothyroxine sodium product is the same as a reference listed drug. Without such information for the Mylan ANDA review, FDA has grounds to withdraw the approval of Mylan's ANDA for levothyroxine, and should initiate such proceedings immediately. The Agency should also not approve any new ANDA until the guidance is issued, or unless the applicant has provided this manufacturing potency and stability data that FDA has deemed essential.

V. Conclusion

Scientific standards for ensuring potency and stability and, therefore, safety and efficacy, for the labeled uses of levothyroxine sodium products, as well as the legal requirements for ensuring that a generic drug is the same as a reference listed drug, require that FDA immediately:

(1) Issue specific guidance for the submission of levothyroxine sodium applications under § 505(j) of the FDCA consistent with current guidance and requirements for levothyroxine sodium products submitted under § 505(b)(2) of the FDCA.

(2) Not approve any ANDA for levothyroxine sodium that fails to conform to the standards for review established for § 505(b)(2) levothyroxine sodium applications.

(3) Withdraw approval of the Mylan ANDA for levothyroxine if it did not meet the required review standard to ensure manufacturing consistency for potency and stability.

ENVIRONMENTAL IMPACT

This petition is entitled to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

ECONOMIC IMPACT

Information regarding economic impact will be submitted on request.

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CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Areta L. Kupchyk, Esq.
Marc Scheineson, Esq.
Counsel to Jerome Stephens Pharmaceuticals, Inc.
Reed Smith L.L.P.
1301 K Street, N.W.
Suite 1100 East Tower
Washington, D.C. 20005
(202) 414-9200